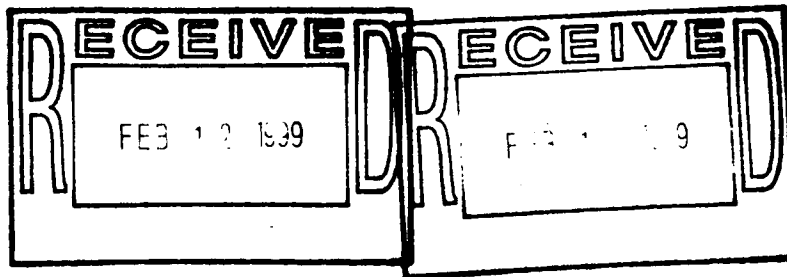


DISTILLED
SPIRITS
COUNCIL
OF THE
UNITED
STATES



February 11, 1999

Dr. Larry G. Hart
Executive Secretary
Board of Scientific Counselors
National Institute of Environmental Health Sciences
Building 101 South Campus, Room A322
111 TW Alexander Drive
Research Triangle Park, North Carolina 27709

Dear Dr. Hart:

Pursuant to the Federal Register notice of December 14, 1998 (Volume 63, Number 239), I am submitting comments regarding the nomination to list beverage alcohol in the National Toxicology Program's (NTP) *Ninth Edition of the Report on Carcinogens* (RoC). On behalf of the Distilled Spirits Council of the United States, Inc. (DISCUS), a national trade association representing producers and marketers of distilled spirits and importers of wines sold in the United States, we appreciate the opportunity to provide this comment.

We fully support and commend the government in providing information to the public about the risks and benefits of beverage alcohol consumption. In so doing, it is critically important that the information be accurate and substantive. NTP has stated that: "Risk assessments are not conducted by the National Toxicology Program for substances in the Report. The listing of a substance in the Report, therefore, does not establish that any such substance presents a risk to persons in their daily lives." (NTP Preamble to the *Eighth Edition of the Report on Carcinogens*) On the other hand, NTP also has stated that its listings "could have broad but indirect effects." (NTP December 3, 1998 Press Release)

Given that the vast majority of Americans who choose to consume beverage alcohol products -- distilled spirits, beer and wine -- do so responsibly and moderately, the potential import of NTP action in the daily lives of these consumers must be taken into account. Beverage alcohol is the first foodstuff that NTP has reviewed since its departure from its traditional role of reviewing occupational or environmental substances for its Report on Carcinogens. Dietary considerations and multiple confounding factors inherent in studies examining beverage alcohol present a new and complex challenge for NTP. This challenge is even greater in the context of dietary substances that have benefits associated with moderate intake.



The proposal pending before the NTP is to make a recommendation to the Secretary of the Department of Health and Human Services as to whether beverage alcohol consumption should be listed in the RoC as a "known human carcinogen." According to NTP's directive, a listing requires a determination whether "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer." Regarding the scientific literature concerning beverage alcohol consumption, Dr. William J. Waddell of the University of Louisville School of Medicine and Dr. Emanuel Rubin of Jefferson Medical College of Thomas Jefferson University, at the request of the beverage alcohol industry, separately have submitted their respective views concerning NTP's proposed action. Dr. Waddell and Dr. Rubin have concluded that NTP has not satisfied its directive and that such a determination cannot be made based upon the underlying literature and NTP proceedings.

Our comments focus upon the procedural flaws that have occurred in NTP's review of beverage alcohol consumption for listing. These flaws include (1) an incomplete review of the literature; (2) the difficulty by the Board of Scientific Counselors Report on Carcinogens Subcommittee (Board Subcommittee) in making a determination on the role of beverage alcohol independent of other confounding factors; and (3) errors and confusion in the Board Subcommittee's proceedings prior to a vote. NTP's first review groups, RG1 and RG2, were not open to the public; therefore, no comment is possible regarding those proceedings.

INCOMPLETE REVIEW

As other federal agencies and the public rely upon the RoC for hazard identification, it is of utmost importance for the review of the literature to be made only after a thorough and exhaustive peer review. In examining the background document and transcript of the December 2nd meeting of the Board Subcommittee, it is clear that this careful review was not fully executed. First, while NTP's literature search uncovered nearly 800 documents published after the 1987 International Agency for Research on Cancer (IARC) listing that was the principal basis for this nomination, only 80 post-1987 studies related to alcohol and cancer were cited in NTP's background document.

No explanation has been provided by NTP as to what selection criteria were employed in disregarding 90 percent of the more recently published studies. Dr. Jameson, Group Leader of the RoC, did note in his remarks at the December 2 meeting that 59 of the largest case control and cohort studies on the consumption of beverage alcohol were evaluated. (Tr. 104-105.) Although studies with the largest sample size may have the most statistical power, size of sample does not necessarily equal the best or even adequate methodology and should not be the sole criterion for selection. Several other factors such as subject selection, variables

considered for examination, adequacy of variable measurement, and the statistical analysis utilized, are but a few additional criteria that generally are used for deciding upon the quality of study results.

These factors, however, did not appear to be considered in study selections. More importantly, it would seem incumbent upon NTP to review all studies that examine a proposed relationship between alcohol and cancer unless there is a specific reason for exclusion.

Second, it appears that NTP relied upon IARC's review of pre-1987 studies without an independent analysis or review. IARC's decision to list alcohol beverages as a human carcinogen was based primarily on studies of heavy drinkers and that also were complicated by the fact that many in the populations studied were, among other things, smokers and had poor nutrient intake and poor oral hygiene. Nevertheless, NTP did not rereview IARC's evaluation of the pre-1987 literature.

We understand that the final vote by IARC was by no means unanimous. Furthermore, IARC's decision has not been followed by agencies considering the question of carcinogenicity and beverage alcohol. In listing chemicals known to the State to cause cancer pursuant to California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65"), the State of California listed beverage alcohol "when associated with alcohol abuse." This listing acknowledges the roles of confounding and consumption levels reflected in the beverage alcohol epidemiological literature.

Third, the last section of NTP's background document consisted of a book chapter (in press) written by Longnecker and Tseng entitled "*Alcohol and Cancer*." While a review document of this kind can be helpful in identifying which studies to examine, it is in no way a substitute for NTP's own careful and exhaustive examination of the underlying literature. Furthermore, in its own mandate, NTP states that only peer-reviewed documents will be used for a determination of listing. A book chapter is not a peer-reviewed document.

Finally, it is not clear from the background document what criteria NTP is using to determine a causal effect of beverage alcohol consumption on cancer sites. Dr. Jameson acknowledged at the December 2 hearing that "there is no adequate experimental animal studies on the carcinogenicity of alcoholic beverage consumption that we could find in any of the literature" and that "the mechanism by which consumption of alcoholic beverages causes cancer in humans is not established." (Tr. 106.) Given the absence of animal evidence support and the lack of any mechanistic explanation, it is all the more incumbent upon NTP to identify the criteria used for its causal determination. Despite a request by Dr. Emanuel Rubin in November 1998 for the criteria used by NTP, no response was forthcoming.

In summary, all available post-1987 literature was not reviewed, adequate selection criteria for literature so excluded were neither identified nor explicated, studies prior to 1987 were not reviewed at all, and part of the background document was not peer-reviewed. Therefore, one must conclude that a thorough and comprehensive review of the literature necessary to make a determination regarding NTP's proposed listing of beverage alcohol was not undertaken, much less completed.

CONFOUNDING FACTORS

It is clear from a review of the December 2, 1998 transcript, that the Board Subcommittee had great difficulty in assessing the role of confounding factors in the studies reviewed for NTP's proposed listing of beverage alcohol as a carcinogen. Dr. Medinsky, one of the Board Subcommittee members and the secondary reviewer for the proposed listing of beverage alcohol, stated:

These individuals also have additional risk factors or confounders which complicate the interpretation of the studies. The confounders are common in a lifestyle typically associated with excessive alcohol consumption, including smoking, inadequate nutrient intake, and viral infection.

Because of the prevalence of these other risk factors in the alcoholic lifestyle, for me it was impossible to separate high alcohol consumption from these other confounders....So I thought that the lifestyle itself was very clear, but I wasn't convinced by alcohol alone. (Tr. 121-122.)

Dr. Medinsky went on to conclude that beverage alcohol should not be listed as a known human carcinogen. (Tr. 124.) Several other members of the Board Subcommittee shared Dr. Medinsky's assessment.

In an effort to reconcile the difficulty in looking at risks associated with beverage alcohol that could not be from other confounding factors such as smoking, Dr. Longnecker, the author of the book chapter in the background document, discussed an article that allegedly examined risks in nonsmoking drinkers. Upon questioning by Dr. Bingham and Dr. Mirer, Dr. Longnecker, however, acknowledged that the cited paper was not part of the background document. (Tr. 139-140.)

Furthermore, Dr. Waddell, who offered public testimony at the hearing, cited data that did not demonstrate an increase in cancer risk associated with nonsmoking drinkers until very high levels of alcohol consumption. At these very high levels, Dr. Waddell noted that it is not

possible to control for other confounding factors associated with an alcoholic lifestyle, such as nutrient intake, viral infection and poor oral hygiene. (Tr. 124-127.)

There was further discussion among members of the Board Subcommittee about the difficulty in evaluating the risk of beverage alcohol given the presence of other confounding factors such as smoking, poor diet, poor oral hygiene, and viral infection; factors known to increase risk of cancers cited in the NTP background document. Despite some Board Subcommittee members stating that they still were confused, Chairman Brown pressed for a vote.

FLAWED REVIEW PROCESS

A careful review of the December 2 transcript demonstrates that the scientific literature on beverage alcohol and cancer was not fully reviewed; procedural problems in voting occurred; and the scientific studies examined were inadequate to determine if beverage alcohol, independent of confounding factors, causes cancer.

First, both the primary reviewer and another Board Subcommittee member admitted that they did not completely review the data. For example, Dr. Friedman-Jimenez stated: "I was not able to review all the studies to make this relatively subtle distinction, but I think it is an important distinction to make." (Tr. 117.) Dr. Friedman-Jimenez was the primary reviewer for the beverage alcohol nomination and was responsible for not only reviewing all studies, but also expertly reporting his analysis to the Board Subcommittee.

Second, a vote was not taken upon all motions offered by the Board Subcommittee members. Dr. Frederick made a motion to amend the proposal in two places. The first motion was a proposal to amend the second sentence of the first paragraph, and the second motion was a proposal to delete a sentence toward the end of the second paragraph. (Tr. 152-53.) Chairman Brown allowed the Board Subcommittee to vote upon Dr. Frederick's first proposed amendment; however, no vote was ever taken on his second proposed amendment, which read as follows:

At the end of the second paragraph, there is a sentence that says, "However, smoking does not explain the observed increased risk of cancers associated with increased alcohol beverage consumption." I am concerned that that statement may be too strong, and I would propose deleting that sentence. (Tr. 153.)

The failure to vote upon Dr. Frederick's second proposed amendment was only one example of the confusion during the deliberations on the beverage alcohol listing. At one point,

Chairman Brown inquired if everyone understood what they were voting upon, and a number of members said "no" or requested clarification. (Tr. 155-157.) Then, after even further confusion among the Board Subcommittee members, Chairman Brown stated:

Good Lord, how many times do I have to say that we are concerned about the final sentence of the first paragraph? Have you got that? Does everybody understand that, because we have to vote on it. All those in favor of the changes--uh-oh. (Tr. 157.)

It was apparent that some members of the Board Subcommittee still were confused; yet, a vote was called. (Tr. 157-165.) At another point, Dr. Henry stated that she did not want to make another motion "because we get so confused by them." (Tr. 165.) In discharging NTP's statutory obligation regarding listing a substance as a known carcinogen, the Chairman should have made every effort to clear up all confusion before voting occurred.

Toward the end of the meeting, Dr. Henry referred to "a number of studies that suggest for low to moderate consumption there are some beneficial effects," and that, since RoC is a publicly communicated document, these are issues to consider. (Tr. 166.) In response, Dr. Zahm and Chairman Brown stated that other substances on the list also have some beneficial effects and they both pointed to tamoxifen. (Tr. 166-167.) They neglected to add, however, that the RG1, RG2 and the Board Subcommittee did not vote to simply list tamoxifen, but unanimously recommended a listing with an additional statement "that there is also conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer." (63 Fed. Reg. 13418, 13420 (March 19, 1998).) From this discussion, it appeared that the Board Subcommittee members were led to believe, however, that a substance currently under consideration -- one that also has risks and benefits -- was proposed for listing as a known human carcinogen without qualification.

CONCLUSION

The mandate of NTP for the Report on Carcinogens is hazard identification. It is clear from the transcript and the background document that an independent examination and analysis of the entire body of the literature pertaining to beverage alcohol was not undertaken, much less completed. Furthermore, confusion was rampant and remained unresolved during the deliberations of the Board Subcommittee, and one motion proposed for a vote still remains pending. Until the foregoing matters are addressed and rectified, NTP should defer any recommendation regarding beverage alcohol. Such a recommendation should not be based upon a process so clearly inadequate and flawed.

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One RG1 member voted against the proposed listing because he/she believed that the listing statement should be for "heavy consumption" of beverage alcohol. (Tr. 163.) Certainly, a number of members of the Board Subcommittee expressed their view that increased risk was associated with an alcoholic lifestyle and smoking combined, as opposed to beverage alcohol consumption alone. Due to the difficulties in separating confounding factors, such as smoking, as well as poor diet, oral hygiene and other factors associated with an alcoholic lifestyle, and the confusion about the ability to statistically correct for these confounders, a thorough examination and analysis of the literature by NTP, at a minimum, are required before action is taken.

The consumption of beverage alcohol products - distilled spirits, beer and wine - has played an accepted role in the cultural and social traditions of American society. Commensurate with this role is the longstanding and continuing commitment by DISCUS members to encourage those adults who choose to drink, to do so responsibly and to combat alcohol abuse. To that end, the industry has joined with government and civic groups in efforts to underscore responsible consumption of its products among adults who choose to drink.

The government plays a critical role in informing the public about the risks and benefits that may be associated with everyday life. This role is an integral part of the fabric of American society. It is for these reasons that we urge NTP to consider carefully its decision so that NTP does not confuse the public and other federal agencies by the listing of beverage alcohol as a human carcinogen based upon inconclusive evidence. To that end, NTP should defer a recommendation until a more careful and thorough analysis of the scientific literature is completed.

Sincerely,


Fred A. Meister
President/CEO

FAM:bca

cc: Dr. C. W. Jameson
Head Report on Carcinogens Group
National Toxicology Program